REMARKS

Applicants have amended the drawings and claims to more particularly define the invention taking into consideration the outstanding Official Action. The objection to the drawings with respect to Figure 5 has been corrected and Applicants submit herewith a corrected Figure 5A and Figure 5B. Accordingly, entry of this sheet of drawing is most respectfully requested and confirmation that it obviates the objection to the drawing in the next Official Action is also requested.

The rejection of claim 4 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out the claimed invention has been carefully considered. It is stated in the Official Action that the claim is rejected because it is not clear if the claim requires a single selection from each of the groups listed or if the assay needs to have only a few of the components listed present in the kit to carry out the method. Claim 4 has been amended to point out that it could be a mixture or a single component as supported by Applicants' specification, page 15, Table 2. The kit contains the necessary components for performing the function of the kit as would be appreciated by one of ordinary skill in the art.

New claims 13-18 have been added to the application to further specific aspects of the invention as fully supported by the specification and claims as originally filed. Claims 13-15 are claims to the support used in the kit. Claims 16-18 are method claims direct to the method of making the novel support used in the kit of the present invention. Applicants most respectfully submit that all of the claims now present in the application are in full compliance with 35 USC 112 and are clearly patentable over the references of record. Accordingly, it is most respectfully requested that this rejection be withdrawn in view of the above clarification.

The rejection of claims 1, 9, 10 and 12 under 35 U.S.C. 102(b) as being unpatentable over Shao et al. has been carefully considered but is most respectfully traversed. In this regard, Applicants wish to direct the Examiner's attention to MPEP

§ 2131 which states that to anticipate a claim, the reference must teach every element of the claim.

> "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). "The identical invention must be shown in as complete detail as is contained in the ... claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed Cir. 1989). The elements must be arranged as required by the claim, but this is not an *ipsissimis verbis* test, i.e., identity of terminology is not required. *In re Bond*, 910 F.2d 831, 15 USPQ2d 1566 (Fed.Cir. 1990).
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> *Akzo N.V. v. International Trade Comm'n*, 808 F.2d 1471, 1 USPQ2d 1241 (Fed. Cir. 1986) (Claims to a process for making aramid fibers using a 98% solution of sulfuric acid were not anticipated by a reference which disclosed using sulfuric acid solution but which did not disclose using a 98% concentrated sulfuric acid solution.).

In the Official Action it is urged that the instant invention is drawn to a kit comprising polyriboadenylic acid and/or polydeoxyadenylic acid bound to a solid surface, the kit further comprising RT-type assay components. It is further urged in the Official Action that Shao et al. disclose the use of a non-radioactive microtiter plate RT-assay in which the immobilized template polyriboadenylic acid is bound to the plate with specific reference to Figure 1. Therefore, it is concluded that the presently claimed invention is anticipated by this reference.

The rejection of claims 1, 4 and 9-12 under 35 U.S.C. 102(b) as being anticipated by Ekstrand et al. has also been carefully considered but is most respectfully traversed. Neither of the references meet the criteria for a proper rejection under 35 USC 102(b) as discussed above and as would be appreciated by one of ordinary skill in the art to which the invention pertains. This is admitted on page 6 of the Official Action wherein it is indicated that the references relied upon in the anticipation

rejections do not disclose the methylimidazole coupling agent which is a claim limitation and cannot be ignored as stated in MPEP section 2113. This section states that the structure implied by the process steps (here the methylimidazole coupling agent) should be considered when assessing the patentability of product-by-process claims over the prior art, especially where the produce can only be defined by the process steps by which the product is made. For this reason alone, these rejections should be withdrawn.

Moreover, Ekstrand et al. describes the construction and properties of a sensitive RT assay, which it is fair to say, uses the same basic concept as the invention. This assay was the state of art when the work with the current invention started.

Shao et al. describes the application of this technology for determination of the RT inhibiting capacity of RT inhibitors and its use for evaluation of their mode of action. This document does not teach any significant improvements of the technique, but refer to the use of the methods described by Ekstrand et al. Shao does further not mention the procedure used for production of the crucial prA coated microtiter plates. This is only commented by Ekstrand et al., which describes the most relevant prior art.

Applicants are aware that the basic concept of the current invention is similar to prior art as described in the documents mentioned above. The current invention, however, provided the crucial innovations for application of this technique for commercial production of RT activity kits. One critical component, which distinguishes the current invention from prior art, is the microtiter plate. Ekstrand et al. does not describe the procedure for production of prA coated microtiter plates, but provides a reference to Suzuki et al. (J.Viol, Meth 1993, 44 p 189-198). The procedure described on page 191 in this document is based on the use of a combination of hydroxysulfosuccinimide and carbodiimide hydrochloride (EDC). Both chemicals are relatively expensive and the procedure is dependent on incubation with prA for 14-18 hours. At least hydroxysulfosuccinimide is sensitive to temperature and moisture and requires special precautions during storage.

In addition, the high reactivity of the reagents used makes it likely that they in addition to perform the intended coupling reaction also to some extent modify the bases in the prA polymer and thereby affecting the polymers ability to serve as template in the polymerase reaction. The plates further require storage in presence of prA and the coupling reagents until needed, and a wash just prior to use.

This makes batch quality control practically impossible! An additional drawback of this method is that the quality of the plates produced fluctuates. A variable proportion of the immobilized prA is according to our experience bound electrostatically. As a result the amount of product recovered after a typical RT reaction is affected by the washing procedures and may vary within and between different plate batches.

The procedure described might be useful for in-house production of research reagents, but not for commercial purposes. The new procedure according to the invention provides a simple, non-toxic; inexpensive method to manufacture large batches prA coated microtiter plates. The new plates are stable during storage, give minimal batch variation and can be delivered ready to use (without requirement of any extra wash prior to use).

Summing up, the procedure described in the current application is not an alternative way of producing prA coated microtiter plates, but a way to produce prA plates with new properties. These properties differs in several crucial aspects from those in prior art as described and/or used by Ekstrand et al., Shao et al. and Suzuki et al. Accordingly, it is most respectfully requested that these rejections be withdrawn.

The rejections of claims 1-4 and 9-12 under 35 U.S.C. 103 as being unpatentable over Shao et al., Ekstrand et al., Suzuki et al. and Rasmussen et al. has been carefully considered but is most respectfully traversed.

Applicants wish to direct the Examiner's attention to the basic requirements of a prima facie case of obviousness as set forth in the MPEP § 2143. This section states that to establish a prima facie case of obviousness, three basic criteria first must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to

modify the reference or to combine the reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Section 2143.03 states that all claim limitations must be taught or suggested by the prior art. In re Royka, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." In re Wilson, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970). If an independent claim is nonobvious under 35 U.S.C. 103, then any claim depending therefrom is nonobvious. In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988).

Applicants also most respectfully direct the Examiner's attention to MPEP § 2144.08 (page 2100-114) wherein it is stated that Office personnel should consider all rebuttal argument and evidence presented by applicant and the citation of In re Soni for error in not considering evidence presented in the specification.

The Examiner further argues that claims 1-4 and 9-12 are obvious when combining the teachings of Ekstrand et al., Shao et al., Suzuki et al. and Rasmussen et al. The three first documents and their relation to the current invention have already been discussed above. The addition of Rasmussen et al. to the panel is clever and takes us to the heart of the matter but is believed to be based on hindsight reconstruction based on Applicants' specification which is impermissible. In re Fritch, 23 USPQ 1780, 1784(Fed Cir. 1992) ("It is impermissible to engage in hindsight reconstruction of the claimed invention, using the applicant's structure as a template and selecting elements from references to fill the gaps.).

Applicants note that a citation from the Examiner's report "Suzuki et al. utilized Covalink plates from NUNC and the coupling agent EDC [1-ethy-3-(3-dimethylaminopropyl)-carboiimide] in N-hydroxysulfosuccinimide to bind the poly A to the bottom of the plate. Rasmussen et al. utilizes the CovaLink NH plates in conjunction

with the coupling agent EDC dissolved in l-methylimidazole. Single stranded DNA has the similar structure to poly dA and poly A, therefore, one of ordinary skill in the art would have had a high expectation of success in applying the EDC coupling agent in l-methylimidazole for the efficient directional binding to the bottom of the plate as taught by Rasmussen et al.". Although, this is what might be expected but only based on Applicants teaching. However, what really happened was that Applicants' attempts to bind prA according to the teachings of Rasmussen and all resulted in plates having bound prA with impaired function as template for reverse transcription! The reason for this was not evaluated in detail, but the results indicate that the method according to Rasmussen et al. is less specific for binding of RNA than of DNA and that the prA was bound also at other positions than at the 5' phosphate group. The reactivity of the EDC makes it also likely that it in addition to perform the intended coupling reaction also to some extent modify the bases in the prA polymer.

Further experiments revealed that the effect of EDC was clearly harmful and that the optimal immobilized prA template was achieved with 1-methylimidazole only. The efficiency of this binding was a function of both pH and imidazole concentration. The procedure was found useful for coupling of prA to CovaLink pates, Nucleolink strips and Nucelolink plates. Further, it was not useful for immobilization of ssDNA primers, which preferentially are immobilized according to Rasmussen et al. The prA bound according to our procedure is not affected by a wash of the plate in 1 M NaCl with 0.2% SDS, which efficiently removes prA unspecifically adsorbed to the plastic.

The prA coated microtiter plates according to the invention are thus superior to prior art as described by Ekstrand et al. and Suzuki et al. or to the corresponding plates produced according to the teachings of Rasmussen et al. A major benefit is the drastically increased assay sensitivity that is achieved with the new plates (demonstrated in table 5 and in examples 1-4). This unexpected effect is partially due to binding of increased amounts of prA according to the new procedure, but also to qualitative differences in the capacity of the bound prA polymer to serve as template for reverse transcription. Applicants do not know what the structural differences between

the prA microtiter plates are. From the literature can be extracted that 1-methylimidazole catalyses the formation of certain organic esters. The exact nature of the prA binding according to the invention is, however, not know, as the procedure does not correspond to methods recommended, or suggested by the manufacturer, or explicitly stated in the literature.

In summary, the new concept for production of prA plates is instrumental for large-scale production of prA coated microtiter plates and drastically improves the detection sensitivity of the RT assays. The assay kit of the invention provides a solid fundament for a new generation of RT activity kit assays. Accordingly, it is most respectfully requested that this rejection be withdrawn.

In view of the above comments and further amendments to the drawings and claims, favorable reconsideration and allowance of all of the claims now present in the application are most respectfully requested.

Respectfully submitted,

BACON & THOMAS, PLLC

By: Richard E Fichter
Richard E. Fichter
Registration No. 26,382

625 Slaters Lane, 4th Fl.
Alexandria, Virginia 22314
Phone: (703) 683-0500
Facsimile: (703) 683-1080

REF:kdd
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February 2, 2004